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Health and Environmental Effects Profile for 1,2-Dibromoethane

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 1,2-DIBROMOETHANE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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16. ABSTRACT

The Health and Environmental Effects Profile for 1,2-dibromoethane was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for 1,2-dibromoethane.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
DNA	Deoxyribonucleic acid
GC	Gas chromatography
i.p.	Intraperitoneal
MS	Mass spectrometry
ppb	Parts per billion
ppm	Parts per million
RNA	Ribonucleic acid
TWA	Time-weighted average

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
DNA	Deoxyribonucleic acid
LD_{Lo}	Lowest dose lethal to recipients
LD_{50}	Dose lethal to 50% of recipients
NOAEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Ethylene dibromide is the common name for 1,2-dibromoethane. Other synonyms for this compound are EDB, ethylene bromide, sym-dibromoethane and glycol bromide (46 FR243, 61671-61676). The structure of 1,2-dibromoethane is given below:

$$Br\text{-}CH_2\text{-}CH_2\text{-}Br$$

Molecular formula: $C_2H_4Br_2$

Molecular weight: 187.9

The Chemical Abstract Service (CAS) Registry number for this compound is 106-93-4.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

1,2-dibromoethane is a colorless, heavy, non-flammable liquid at room temperature with a characteristic mildly sweet odor detectable in the air at levels ranging from 10-25 ppm (46 FR243, 61671-61676). Some of the physical properties of 1,2-dibromoethane are given below (42 FR240, 63136; IARC, 1977).

Melting Point:	9.97°C
Boiling Point:	131.6°C
Density at 20°C:	2.19 g/mℓ
Vapor pressure at 25°C:	11.0 mm of Hg
Vapor density (air = 1):	6.5
Density in saturated air (air = 1):	1.08
Viscosity at 20°C:	1/65 cp
Solubility in water at 30°C:	430 mg/ℓ
Conversion factor:	1 ppm ~7.68 mg/m³

1,2-Dibromoethane is soluble in ethanol and ethyl ether. It reacts as an alkylating agent liberating bromide (IARC, 1977). This compound is stable under ordinary conditions. Slight decomposition may occur on exposure to light. It slowly forms vinyl bromide on contact with a warm alkaline solution, and it reacts violently with liquid ammonia when the mixture is allowed to reach room temperature (Stenger, 1978).

1.3. PRODUCTION DATA

1,2-Dibromoethane (ethylene dibromide) is manufactured by the addition of bromide to ethylene as represented by the following reaction:

$$Br_2 + CH_2 = CH_2 \rightarrow BrCH_2CH_2Br$$

The producers of 1,2-dibromoethane (SRI, 1982) and the production ranges listed in the U.S. EPA (1977) TSCA production inventory, are summarized below:

Producer	Location	Production Range (million lbs/year)
Dow Chemical	Magnolia, AR	50-100
Ethyl Corp.	Magnolia, AR	100-500
Great Lakes Chem. Corp.	El Dorado, AR	-
Ameribrom, Inc.	(importer)	-
Mobil Oil Co.	New York, NY	0.1-1.0
PPG Industries, Inc.	Beaumont, TX	-

According to a 1981 U.S. EPA estimate, ~340-360 million pounds of 1,2-dibromoethane were produced in the U.S. annually (46 FR243, 61671-61676).

1.4. USE DATA

Dibromoethane is used as a gasoline additive in preventing lead fouling from tetraalkyl lead antiknock agents. In 1963 dibromoethane accounted for

77% of the bromide produced in the United States, however, the percentage is steadily decreasing because of U.S. EPA regulations requiring the reduction of lead emissions from automobiles (Stenger, 1978).

1,2-Dibromoethane has also been used as a fumigant for grains, fruits and vegetables (Metcalf, 1978), as an anticatalyst or inhibitor of the oxidation of ethylene to carbon dioxide and a catalyst for ethylene dichloride (Shultze, 1971) and as an activator of magnesium in the Grignard reaction (Waugh, 1971).

In addition, 1,2-dibromoethane is used as an intermediate in the synthesis of dyes and pharmaceuticals, and as a solvent for resins, gums and waxes (46 FR 243, 61671-61676).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

No comprehensive study pertaining to the atmospheric fate and transport of 1,2-dibromoethane is available. The photoabsorption cross sections for 1,2-dibromoethane in the wavelength region of 190-270 nm were studied by Uthman et al. (1978). No photochemical studies, however, have been reported on this compound in the tropospheric solar wavelength region, (i.e., wavelength >290 nm). Using thermodynamic data, Uthman et al. (1978) predicted that photo-dissociation of ethylene dibromide is energetically possible at wavelength >290 nm. The possibility of decomposition of this compound from exposure to light was also speculated by Johns (1976).

1,2-Dibromoethane may react slowly to atmospheric peroxides and ozone, typically showing half-lives toward these reactions to be >100 days (Johns, 1976). The reactions of hydroxyl radicals with 1,2-dibromoethane may be faster. The half-life for this reaction has been estimated to be ~32 days (Howard and Evenson, 1976; Singh et al., 1981).

Because of its relatively high vapor pressure at ambient temperature (11 mm of Hg at 25°C) and low soil sorption coefficient (Chiou et al., 1979), 1,2-dibromoethane is expected to exist predominantly in the vapor phase in the atmosphere. This was confirmed by Going and Spigarelli (1975), who found a small percent (<0.02% to >10%) of total 1,2-dibromoethane in the atmosphere to be in the particulate form. Most of the compound was found to be present in the vapor phase.

The transport of 1,2-dibromoethane in the atmosphere from chemical manufacturing plants has been determined both experimentally and theoretically (Johns, 1976). Using a Gaussian plume equation of Turner to predict downwind atmospheric levels of this chemical in the surrounding atmosphere, Johns (1976) estimated a concentration of 6.3 $\mu g/m^3$ for dibromoethane at

a distance of 500 m downwind from a plant with an emission rate of 0.00262 g/sec and at a wind velocity of 6 m/sec. Therefore, this compound is expected to be transported to reasonable distances from the sites of emissions. Going and Spigarelli (1976) experimentally detected 1,2-dibromoethane as far as 1 mile downwind from a fumigation center. Both dry and wet deposition may remove 1,2-dibromoethane from the atmosphere. Because most of the atmospheric 1,2-dibromoethane is expected to be present in the vapor phase as opposed to particulate phase, however, removal by rainwater seems to be a more likely process. Going and Spigarelli (1976) experimentally detected 1,2-dibromoethane in dust fall (6-363 pg/cm^2/hr) and rainwater (1 µg/ℓ) from fumigation facilities.

Of the three chemical processes that may degrade/transform 1,2-dibromoethane in aquatic media, the fate of this chemical with respect to hydrolytic reaction is the best studied. The hydrolysis half-life for 1,2-dibromoethane in neutral aquatic media at ambient temperature has been reported to be 5-10 days (Johns, 1976). The fate of this chemical with respect to free radical reactions in aquatic media is not available. Similarly, the possible aquatic photolytic reaction rate of 1,2-dibromoethane with available sunlight is unknown.

The biodegradation rates of 1,2-dibromoethane in aquatic media have not been studied. Judging from the relatively slow biodegradation of this chemical in soils (Castro and Belser, 1968), however, it can be speculated that biodegradation may not be a significant fate process for this chemical in aquatic media.

The transport of 1,2-dibromoethane from water to particulate matter in water and their subsequent partial precipitation to sediment may not be a significant process. This speculation is based on the weak sorption capac-

ity of this compound in soil and the relatively high solubility in water. Decarlo (1979) reported the detection of 1,2-dibromoethane in sediment from surface water near a manufacturing site in Arkansas. The transport of aquatic 1,2-dibromoethane by way of evaporation appears to be a more significant process than adsorption. The half-life for evaporation was estimated to be 6.8 minutes for a 0.1 ppm stirred solution at 24°C and a depth of 1.6 cm (Chiou et al., 1980). With mass transfer coefficient correlation data, MacKay and Yeun (1983) estimated the evaporation half-life for 1,2-dibromoethane from 1 m depth of water at a wind velocity of 8.6 m/sec to be 4.3 hours.

No experimental data on the bioconcentration of this chemical by aquatic organisms are available. From binary regression equations, Kenaga (1980) predicted a BCF of 2-6 for this chemical. Therefore, this compound is not expected to bioaccumulate in aquatic organisms.

The fate of 1,2-dibromoethane in soils is likely to be controlled by its ability to undergo chemical and biological reactions. None of the three chemical reactions (hydrolysis, radical oxidation and photochemical reaction) that may be responsible for the disappearance of this chemical from soil are thoroughly studied. It has been reported that hydrolysis of this chemical in soils may not be a significant process (Ross et al., 1978). The significance of photolysis and radical oxidation of this compound in soil in determining the fate of this chemical has not been studied.

Available data indicate that soil microorganisms may slowly biodegrade this compound. For example, Castro and Belser (1968) found that 97% of 1,2-dibromoethane can be degraded in 4 weeks by soil-water culture at a 1,2-dibromoethane concentration of 5.8×10^{-4}M and a pH of 7. The products

of biodegradation are ethylene and bromide ions. The effect of 1,2-dibromoethane on soil microorganisms also has been studied. Although this compound may decrease the ammonification and nitrification process in soils initially, it does not affect or is slightly favorable to the microbial process in soils a few days after application (Ampova and Stefanov, 1981).

The two important processes that may control the transport of 1,2-dibromoethane in soils are volatilization and leaching. Both processes are related to the absorption capacity of this chemical to soil. The soil absorption coefficient for this compound standardization with respect to soil organic matter content is ~36 (Chiou et al., 1979). Rogers and McFarlane (1981) found that <6% of this compound in the aquatic phase was absorbed by soil and clay. Therefore, this compound is not strongly sorbed to soils and may be amenable to both volatization and leaching to surface and groundwater. Although no comprehensive study has been done to establish the rates of the two processes from soils, indirect evidence indicates that small amounts of 1,2-dibromoethane may be lost from soils to the atmosphere via volatilization (Ross et al., 1978) and will be transported to surface water via runoffs and to groundwater via leaching (Page, 1981). McKenry and Thomason (1974) first attempted a material balance for 1,2-dibromoethane after application to soil. They found that after 3 days of application at 15°C, ~40, 25 and 20% remained in the soil, soil-water and liquid phase, respectively. While 15% remained unaccounted for after 3 days, the value became 40% after 10 days. Undoubtedly, biodegradation, volatilization and leaching are responsible for the loss of 1,2-dibromoethane from the soil.

3. EXPOSURE

1,2-Dibromoethane is ubiquitous in the atmosphere. In general, the atmospheric concentrations of 1,2-dibromoethane around the various sources decrease in the following order: manufacturing sites, fumigation centers, retail gasoline stations, urban high-traffic areas, suburban low traffic areas and rural sites. Margler et al. (1979) identified 1,2-dibromoethane as 1 of 11 chemicals of greatest potential concern in California as airborne carcinogens. The atmospheric levels of 1,2-dibromoethane at various locations are shown in Table 3-1. The atmospheric concentration of 1,2-dibromoethane in London, England, was found to range between 0.001 and 0.17 $\mu g/m^3$ and outside of a garage in London, England, was 1.2 and 1.8 $\mu g/m^3$ (Leinster et al., 1978). The concentration of 1,2-dibromoethane around Gatwick airport, London, was determined to range from undetectable to 0.22 $\mu g/m^3$ (Tsani-Bazaca et al., 1982). Hasanen et al. (1979), however, failed to detect any 1,2-dibromoethane in the exhaust of automobiles using Finnish 99-octane gasoline containing 0.59 g/ℓ of lead. The high detection limit of 50 $\mu g/m^3$ reported in these surveys may be the reason for the failure to detect 1,2-dibromoethane.

In a recent report (Brodzinsky and Singh, 1982), the ambient atmospheric data for 1,2-dibromoethane in various locations in the United States were assessed. The mean atmospheric concentrations of 1,2-dibromoethane in rural/remote, urban/suburban and source areas in the United States were 0.014, 0.24 and 9.22 $\mu g/m^3$, respectively.

The occupational exposure to 1,2-dibromoethane at two manufacturing and two user industries was monitored by Oser (1980). The 8-hour median total weighted average exposures range from 10-500 ppb. The short-term median ceiling level concentrations ranged from 0.1-12.0 ppm. It was also

TABLE 3-1

Atmospheric Concentrations of 1,2-Dibromoethane at Selected Sites

Site	Year Sampled	Concentration (µg/m³)		Reference
		Range	Mean	
Continental Oil Co., Ponca City, OK	1976	0.05-0.13	0.07	Going and Spigarelli, 1976
Mobil Oil Co., Paulsboro, NJ	1976	0.09-0.20	0.12	Going and Spigarelli, 1976
Retail Gasoline Station, Phoenix, AZ	1976	0.19-0.50	0.30	Going and Spigarelli, 1976
Retail Gasoline Station, Los Angeles, CA	1976	0.09-0.18	0.11	Going and Spigarelli, 1976
Retail Gasoline Station, Camden, NJ	1976	0.38-0.49	0.45	Going and Spigarelli, 1976
Highly trafficked, Phoenix, AZ	1976	0.31-0.44	0.36	Going and Spigarelli, 1976
Highly trafficked, Los Angeles, CA	1976	0.11-0.16	0.12	Going and Spigarelli, 1976
Suburban, Kansas City, MO	1976	0.061	0.06	Going and Spigarelli, 1976
Rural, Maryville, MO	1976	0.07	0.07	Going and Spigarelli, 1976
Fumigation Center, Wahneta, FL	1976	0.09-29.3	3.79	Going and Spigarelli, 1976
Fumigation Center, Ft. Pierce, FL	1976	0.09-85.4	8.98	Going and Spigarelli, 1976
Dow Manufacturing Plant, Magnolia, AR	1975	105-115	0	Going and Long, 1975
Ethyl Corp. Manufacturing Plant, Magnolia, AR	1975	4.2-90.2	5.8	Going and Long, 1975

TABLE 3-1 (cont.)

Site	Year Sampled	Concentration (µg/m³)		Reference
		Range	Mean	
Rural Area, Pullman, WA	NS	detected		Harsch et al., 1979
Los Angeles, CA	1979	0.04-1.44	0.25	Singh et al., 1981
Phoenix, AZ	1979	0.02-1.57	0.31	Singh et al., 1981
Oakland, CA	1979	0.02-0.65	0.12	Singh et al., 1981
Houston, TX	1980	0.08-2.88	0.45	Singh et al., 1982
St. Louis, MO	1980	0.06-0.20	0.12	Singh et al., 1982
Denver, CO	1980	0.08-0.60	0.24	Singh et al., 1982
Riverside, CA	1980	0.08-0.36	0.17	Singh et al., 1982
Staten Island, NY	1981	0.09-0.28	0.15	Singh et al., 1982
Pittsburgh, PA	1981	0.05-0.45	0.12	Singh et al., 1982
Chicago, IL	1981	0.05-1.91	0.20	Singh et al., 1982
Various locations in NJ	1979	ND[a]-42.2 (0.08)	7.5[b]	Bozzelli et al., 1980

[a] ND = Not detected with detection limit given in parenthesis

[b] This is the average value of all samples with concentrations >0.08 µg/m³.

NS = Not specified

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determined that during normal plant operations the greatest potential for exposure to 1,2-dibromoethane was related to open system processes and, more specifically, the time at which quality control samples were taken.

The concentrations of 1,2-dibromoethane in aqueous effluent stream and runoff water have been determined by Going and Spigarelli (1976) as shown in Table 3-2. Representative groundwater and surface water samples from different locations in New Jersey were collected and analyzed for 1,2-dibromoethane (Page, 1981). The compound was found in 8% of all groundwater and 6% of all surface water. The highest concentrations of 1,2-dibromoethane in groundwater and surface water were 48.8 and 0.2 µg/ℓ, respectively. Similarly, Burmaster (1982) determined that the concentration of 1,2-dibromoethane in a few drinking water wells in Hawaii and California ranged from 35-300 µg/ℓ. STORET contains four aquatic monitoring data for 1,2-dibromoethane. All samples were obtained from aquifers in Minnesota and contained this compound at a concentration of <0.5 µg/ℓ.

The concentration of 1,2-dibromoethane in soil from the fumigation center at Ft. Pierce, Florida, ranged between 0.4 and 3.4 ng/g (Ross et al., 1978). Residue levels of 1,2-dibromoethane in food samples fumigated with this compound also have been investigated. Berck (1974) determined the level of this compound in flour to be 0.01-0.29 ppm. When apples were fumigated at 8-24 mg/ℓ of 1,2-dibromoethane for 4 hours at 13°C, the level of this compound in the edible portion was <0.1 ppm in <13 days (Dumas and Bond, 1975). Similarly, when oranges were fumigated at 24 g/m³ of 1,2-dibromoethane at 20°C for 2 hours, subsequently held at 20°C for 24 hours, and then stored at 6°C, no detectable level of this compound was found in 28 days (Singh et al., 1979). 1,2-Dibromoethane has also been detected in foods taken from the school lunch program at concentration ranges of <8 ppb

TABLE 3-2

Concentrations of 1,2-Dibromoethane in a Few Aqueous Samples*

Site	Year Sampled	Nature of Sample	Concentration in Range (µg/ℓ)
Continental Oil Co., Ponco City, OK	1976	water from treatment plant outlet	0.14-0.17
Retail Gasoline Station Los Angeles, CA	1976	runoff water	0.11-0.17
Fumigation Center, Ft. Pierce, FL	1976	runoff water	0.9-2.0

*Source: Going and Spigarelli, 1976

to 4 ppm and <0.5 ppb to 0.26 ppm in the flour and biscuit samples, respectively (Rains and Holder, 1981). The determination of volatile halocarbon in Total Diet Market Basket was conducted recently by the U.S. Food and Drug Administration (Entz et al., 1982). Thirty-nine different food items were purchased at retail markets and were composited for analysis into four groups representing dairy products; meat, fish and poultry; oils, fats and shortening; and beverages. 1,2-Dibromoethane was not detected in any of the food composites, however, the quantitation limits were 48.5, 84, 92 and 5.8 ppb for the dairy composites, meats, oils and fats, and beverages, respectively.

4. PHARMACOKINETICS

The pharmacokinetics of 1,2-dibromoethane in laboratory animals have been reported by many investigators, and reviews are available (NIOSH, 1977a, 1980; Rannug, 1980). Progress has been made toward understanding the biochemical mechanisms by which 1,2-dibromoethane is removed from the body. Glutathione conjugation plays a major role in 1,2-dibromoethane metabolism, but may form toxic intermediates and cause depletion of liver glutathione. The intermediates, 2-bromoacetaldehyde and S-2-bromoethyl glutathione, are reported to bind to biomacromolecules and induce mutagenesis, respectively. They are ultimately converted into cysteine conjugates, and their urinary excretion has been observed to follow first order elimination kinetics.

4.1. ABSORPTION

The fate of inhaled radiolabeled [^{14}C]-1,2-dibromoethane vapors was examined in Sprague-Dawley rats by Watanabe et al. (1977, 1978). Blood levels of 1,2-dibromoethane during and following exposure to atmospheres containing 78 ppm of the compound for 6 hours rose quickly and then leveled off at 0.78 µg/mℓ within the first hour of exposure. Blood levels following exposure to 6 ppm for 7 hours took longer (~6 hours) to reach a steady state of 0.067 µg/mℓ. Upon percutaneous exposure to 1 mℓ of liquid 1,2-dibromoethane in glass depots attached to guinea pigs for 6 hours, a similar rise in blood concentration was observed by Jakobson et al. (1982). A concentration of 2 µg/mℓ was observed within the first hour of exposure and remained relatively constant for the remaining 5 hours of exposure. Apparently the absorption of 1,2-dibromoethane into the blood during inhalation or dermal administration at these dose levels is largely in equilibrium with the elimination from the blood.

4.2. DISTRIBUTION

Distribution of radiolabeled 1,2-dibromoethane in the tissues of the guinea pig has been investigated by Plotnick and Conner (1976). A single i.p. injection of 30 mg [^{14}C]-1,2-dibromoethane/kg was given to each of 18 guinea pigs. Three animals were killed at intervals of 4, 8, 12, 24, 48 and 72 hours post-administration and their tissues removed, digested and assayed for radioactivity. The highest levels of radioactivity were found in the kidneys, liver and adrenal glands at all time intervals.

Shih (1976) administered [^{14}C]-dibromoethane to rats and mice by i.p. injection and measured the distribution of radioactivity of the tissues 1, 3 and 24 hours after administration. The highest levels of radioactivity were found in the liver, kidney and small intestine 1-3 hours after injection. Irreversibly bound radioactivity was found in the liver and kidney 24 hours after injection. Hill et al. (1978) also reported finding the highest levels of radioactivity bound to protein in the kidneys and livers of rats given a single i.p. injection of [^{14}C]-1,2-dibromoethane.

Rapid removal from circulation and little generalized distribution of [^{14}C]-1,2-dibromoethane were observed by Edwards et al. (1970). Male RF/Hiraki mice were given 40 mg/kg of labeled 1,2-dibromoethane by i.p. injection and were killed 1, 2, 3 or 24 hours post-injection whereupon their tissues and excreta were assayed for radioactivity. No unchanged 1,2-dibromoethane was found in the urine, but the metabolites S-(2hydroxyethyl)-cysteine, S-(2-hydroxyethyl)-cysteine-N-acetate and S-(2hydroxyethyl)-cysteine-N-acetate-S-oxide were identified. One hour after administration, the small intestine, liver, kidney and fat contained appreciable amounts of radioactivity (i.e. 34, 12, 13 and 4.9% of the dose). Radioactivity levels

in the tissues fell to <1% by 24 hours in all tissues except blood. Rapid removal from blood by the liver with excretion in the bile accounted for 5% of the dose administered.

Watanabe et al. (1977, 1978) found the highest levels of radioactivity in the kidneys and livers of rats following inhalation exposure of 7, 25 and 75 ppm of [^{14}C]-1,2-dibromoethane.

4.3. METABOLISM

As reviewed by Rannug (1980), the metabolism of 1,2-dibromoethane has been studied extensively and pathways by which it is eliminated have been proposed. Conjugation of 1,2-dibromoethane with glutathione and subsequent urinary excretion as mercapturic acid derivatives is thought to be one of the primary mechanisms of elimination (Nachtomi et al., 1966; Edwards et al., 1970). Depletion of liver sulfhydryl groups upon oral administration of 1,2-dibromoethane (Nachtomi et al., 1968) in rats lends support to this proposed mechanism. Enzymes (glutathione S-transferases) identified in rat liver homogenate were found to catalyze the reaction of glutathione and 1,2-dibromoethane in vitro (Nachtomi et al., 1968).

Kluwe et al. (1981) reported the ability of 1,2-dibromoethane to deplete non-protein sulfhydryl (mostly glutathione) contents in various tissues of rats and mice following i.p. administration. Male ICR mice and F344 rats received a single i.p. injection of 1,2-dibromoethane/kg and preliminary studies showed that maximum depletion of non-protein sulfhydryl groups occurred 2 hours after administration. Thus, animals were killed 2 hours post-exposure and their lungs, kidneys, liver, testes and stomach were removed for determination of non-protein sulfhydryl (NPS) concentration. Dose-related decreases in NPS concentration in the livers of treated rats and in the kidneys of treated mice were observed. Lung, testicular and

stomach NPS content was reduced by 1,2-dibromoethane, but not to the same degree as in the kidneys and liver. This result is expected, considering the mode of distribution of a toxicant administered by i.p. injection (i.e., routing through the liver into systemic circulation, which perfuses the kidneys at a greater rate than the stomach and testes).

A second biochemical reaction occurring in the liver is thought to dehalogenate 1,2-dibromoethane by oxidation, forming the reactive intermediate, 2-bromoacetaldehyde. This reaction is catalyzed by an enzyme in hepatic microsomes (Van Dyke and Wineman, 1971). The formation of this intermediate can explain the irreversible binding of radiolabeled 1,2-dibromoethane to biomacromolecules in vivo and in vitro (Hill et al., 1978; Shih and Hill, 1981).

An experiment designed to elucidate the mechanism by which 1,2-dibromoethane is conjugated with glutathione was conducted by Van Bladeren et al. (1981). Tetradeutero-1,2-dibromoethane (0.1 mmole) was given to 3 male rats by i.p. injection and 4 male and 4 female rats orally. Urine of dosed animals was collected and the various metabolites it contained were determined by GC-MS. The authors reasoned that if 1,2-dibromoethane is directly conjugated with glutathione to form a reactive intermediate, then no carbon/deuterium bonds would be broken in the resulting mercapturic acid metabolite. On the other hand, the breakage of 3 carbon/deuterium bonds in tetradeutero 1,2-dibromoethane metabolites would indicate that it was oxidized to 2-bromoacetaldehyde (loss of one deuterium atom) with subsequent enolization (where 2 more deuterium atoms are removed) and then conjugation with glutathione. Examination of the mercapturic acid derivatives isolated from treated rat urine showed that most of the metabolites contained one deuterium atom (~60%). About 22% of the metabolites contained 4 deuterium atoms

and minor amounts of isomers containing 2 or 3 deuterium atoms. These results show that in the metabolism of 1,2-dibromoethane in the rat, the oxidative and conjugative pathways occur in a ratio of ~4:1. In the direct conjugation mechanism, the reactive conjugate, S-2-bromo-ethyl-glutathione is formed and in the oxidative mechanism, the reactive 2-bromoacetaldehyde is formed. Both of these intermediates can undergo further conversion and can ultimately appear as the mercapturic acid derivative, N-acetyl-S-2-hydroxyethyl-L-cysteine in the urine.

Lack of mutagenic activity was reported for 2-bromoacetaldehyde in a reversion assay using S. typhimurium TA1535 (Rosenkranz, 1977). Increased mutagenic activity of 1,2-dibromoethane towards E. coli and S. typhimurium was demonstrated by Van Bladeren et al. (1980) when rat liver S100 supernatant (containing soluble glutathione-S-transferases) and glutathione were included in the incubation mixture. Direct conjugation of 1,2-dibromoethane to the reactive intermediate S-2-bromoethyl-glutathione is thought to account for the increased mutagenicity.

4.4. EXCRETION

In the tissue distribution study in guinea pigs of Plotnick and Conner (1976), urinary excretion was found to account for 66% of the dose 72 hours after administration. Fecal excretion represented <3% of the dose in the same time period. Unchanged 1,2-dibromoethane apparently was present in the expired air and represented 10-12% of the dose.

Watanabe et al. (1977, 1978) also reported urinary excretion accounting for most (80%) of the 1,2-dibromoethane recovered from rats 48 hours post-exposure. The rates of excretion followed first order kinetics and produced half-lives of 5.1, 5.5 and 5.6 hours for the exposure levels 7, 25 and 75 ppm, respectively.

Edwards et al. (1970) reported the absence of unchanged 1,2-dibromoethane in the urine 24 hours after i.p. injection, but urinary metabolites and biliary metabolites reflected 40 and 5% of the total dose excreted at this time interval.

5. EFFECTS

5.1. CARCINOGENICITY

5.1.1. Animal Studies. Carcinogenicity bioassays using rats and mice suggest that 1,2-dibromoethane induces increased tumor incidence at the site of contact and in distant sites following oral, inhalation and dermal exposures. These studies have been reviewed (U.S. EPA, 1982) and are summarized in Tables 5-1 through 5-5, as presented in that document. IARC (1977) stated that 1,2-dibromoethane is carcinogenic to rats and mice.

5.1.1.1. ORAL ADMINISTRATION -- Osborne-Mendel rats received TWA doses of 26-29 mg 1,2-dibromoethane/kg bw/day by gavage for 49 weeks (male) or 61 weeks (female) (NCI, 1978). Significantly increased incidences of squamous cell carcinomas of the stomach (both sexes), hepatocellular carcinomas and neoplastic nodules of the liver (female) and hemangiosarcomas of the circulatory system (males) were observed upon histopathological examination in 20-90% of the treated rats with no tumors observed in control rats (Table 5-1). High treatment-related mortality prompted alterations in the dosing regimen, resulting in similar TWA dosages for high and low treatment groups and an early termination of the study.

Male and female B6C3F1 mice received TWA doses of 44 or 76 mg 1,2-dibromomethane kg/bw by gavage for 53 weeks (NCI, 1978). Significantly increased incidences of squamous-cell forestomach carcinomas and alveolar/bronchiolar adenomas were observed upon histopathological examination in 56-94% of the treated mice, with no tumors observed in control rats (Table 5-1). Similar high treatment-related mortality with dosing regimen alterations and early termination of the study were experienced, as in the rat bioassay.

TABLE 5-1

Summary of Oral Carcinogenicity Bioassay of 1,2-Dibromoethane[a]

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound[b]	Target Organ	Tumor Type	Tumor Incidence[c] (P value)
Rats/ Osborne-Mendel	M	29 mg/kg/day[d]	49 wk	49 wk	96.3-99.6%	forestomach	carcinoma[e]	33/50 (P<0.001)
						circulatory system	hemangiosarcomas	4/27[f] (N.S.)
Rats/ Osborne-Mendel	M	27 mg/kg/day[d]	49 wk	49 wk	96.3-99.6%	forestomach	carcinoma	45/50 (P<0.001)
						circulatory system	hemangiosarcoma	11/50[f] (P=0.018)
Rats/ Osborne-Mendel	M	0 mg/kg/day (vehicle control)	49 wk	63 wk	NA	forestomach	carcinoma	0/20 (P<0.001)
						circulatory system	hemangiosarcoma	0/20[f] (N.S.)
Rats/ Osborne-Mendel	F	28 mg/kg/day[d]	61 wk	61 wk	96.3-99.6%	forestomach	carcinoma[e]	29/50 (P<0.001)
						liver	carcinoma[g]	5/25[f] (P=0.043)
							carcinoma/nodules[g,h]	6/25[f] (P=0.022)
Rats/ Osborne-Mendel	F	26 mg/kg/day[d]	61 wk	61 wk	96.3-99.6%	forestomach	carcinoma	40/50 (P<0.001)
						liver	carcinoma	1/35[f] (N.S.)
							carcinoma/nodules	1/35[f] (N.S.)
Rats/ Osborne-Mendel	F	0 mg/kg/day (vehicle control)	61 wk	63 wk	NA	forestomach	carcinoma	0/20 (P<0.01)
						liver	carcinoma	0/20[f] (P=0.028)
							carcinoma/nodules	0/20[f] (P=0.014)

TABLE 5-1 (cont.)

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound[b]	Target Organ	Tumor Type	Tumor Incidence[c] (P value)
Mice/ B6C3F1	M	76 mg/kg/day[d]	53 wk	77 wk	96.3-99.6%	forestomach	carcinoma[e]	29/49 (P<0.001)
						forestomach	papilloma or carcinoma[e]	3/149 (P<0.001)
						lung	adenoma[1]	(10/47 (P=0.021)
Mice/ B6C3F1	M	44 mg/kg/day[d]	53 wk	77 wk	96.3-99.6%	forestomach	carcinoma	45/50 (P<0.001)
						forestomach	papilloma or carcinoma	45/50 (P<0.001)
						lung	adenoma	4/45 (N.S.)
Mice/ B6C3F1	M	0 mg/kg/day (vehicle control)	53 wk	59 wk	NA	forestomach	carcinoma	0/20 (P=0.003)
						forestomach	papilloma or carcinoma	0/20 (P=0.001)
						lung	adenoma	0/20 (P=0.009)
Mice/ B6C3F1	F	76 mg/kg/day[d]	53 wk	80 wk	96.3-99.6%	forestomach	carcinoma[e]	28/50 (P<0.001)
						lung	adenoma[1]	4/14[f] (P=0.024)
Mice/ B6C3F1	F	44 mg/kg/day[d]	53 wk	78 wk	96.3-99.6%	forestomach	carcinoma	46/49 (P<0.001)
						lung	adenoma	2/10[f] (N.S.)
Mice/ B6C3F1	F	0 mg/kg/day (vehicle control)	53 wk	60 wk	NA	forestomach	carcinoma	0/20 (P=0.011)
							adenoma	0/19[f] (P=0.018)

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TABLE 5-1 (cont.)

QUALITY OF EVIDENCE

Strengths of Study: The compound was administered by a natural route of exposure to two species of animals. Comprehensive pathologic examinations were performed.

Weakness of Study: Poor survival in both species necessitated early termination of the study. Early mortality in the high-dose rats prompted a 13-week dose suspension after 16 weeks, and a subsequent resumption of treatment at the same dosage that the low dose rats were receiving, resulting in comparable TWA doses for both the high and low dose rats.

Overall Adequacy: Adequate

[a]NCI, 1978

[b]Vehicle was corn oil (intubation) in all cases

[c]Incidences of most frequently appearing tumors were tabulated. The probability levels for the Fischer exact and Cochran-Armitage tests are given beneath the incidence of tumors in the treated groups and control group, respectively, when P<0.05; otherwise, N.S. (not significant) is indicated.

[d]Reported time-weighted average doses were multiplied by 5/7 to give a more accurate daily dose (the reported TWA doses reflected gavage treatment on 5 consecutive days/week).

[e]Squamous-cell carcinomas

[f]Time-adjusted incidence because of early mortality

[g]Hepatocellular carcinomas

[h]Preneoplastic nodules

[i]Alveolar/bronchiolar adenomas

NA = Not applicable

TABLE 5-2

Summary of Inhalation Carcinogenicity Bioassay of 1,2-Dibromoethane[a]

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[b] (P value)
Rats/F344	M	40 ppm[c]	88 wk	88-89 wk	99.3-99.4%	vapor	nasal cavity	carcinoma	21/50 (P<0.001)
								adenocarcinoma	28/50 (P<0.001)
								tumors[d]	41/50 (P<0.001)
							circulatory system	hemangiosarcomas	15/50 (P<0.001)
							tunica vaginalis	mesothelioma or malignant	25/50 (P<0.001)
Rats/F344	M	10 ppm[c]	103 wk	104 wk	99.3-99.4%	vapor	nasal cavity	carcinoma	0/50 (N.S.)
								adenocarcinoma	20/50 (P<0.001)
								tumors	39/50 (P<0.001)
							circulatory system	hemangiosarcomas	1/50 (N.S.)
							tunica vaginalis	mesothelioma or malignant	8/50 (P=0.015)
Rats/F344	M	0 ppm[e] (chamber control)	NA	104-106 wk	NA	ambient air	nasal cavity	carcinomas	0/50 (P<0.001)
								adenocarcinoma	0/50 (P<0.001)
								tumors	0/50 (P<0.001)
							circulatory system	hemangiosarcomas	0/50 (P<0.001)
							tunica vaginalis	mesothelioma or malignant	1/50 (P<0.001)

TABLE 5-2 (cont.)

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[b] (P value)
Rats/F344	F	40 ppm[c]	91 wk	91-92 wk	99.3-99.4%	vapor	nasal cavity	carcinoma	25/50 (P<0.001)
								adenocarcinoma	29/50 (P<0.001)
								tumors[d]	43/50 (P<0.001)
							lung	carcinoma/adenoma[f]	5/47 (P=0.024)
							circulatory system	hemangiosarcoma	5/50 (P=0.028)
							mammary gland	fibroadenoma	24/50 (P<0.001)
Rats/F344	F	10 ppm[c]	103 wk	104 wk	99.3-99.4%	vapor	nasal cavity	carcinoma	0/50 (N.S.)
								adenocarcinoma	20/50 (P<0.001)
								tumors	34/50 (P<0.001)
							lung	carcinoma/adenoma	0/48 (N.S.)
							circulatory system	hemangiosarcoma	0/50 (N.S.)
							mammary gland	fibroadenoma	29/50 (P<0.001)

TABLE 5-2 (cont.)

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[b] (P value)
Rats/F344	F	0 ppm[e] (chamber control)	NA	104-106 wk	NA	ambient air	nasal cavity	carcinoma	0/50 (P<0.001)
								adenocarcinoma	0/50 (P<0.001)
								tumors	1/50 (P<0.001)
							lung	carcinoma/adenoma	0/50 (P=0.001)
							circulatory system	hemangiosarcoma	0/50 (P=0.002)
							mammary gland	fibroadenoma	4/50 (P=0.002)
Mice/B6C3F1	M	40 ppm[c]	78 wk	78-79 wk	99.3-99.4%	vapor	lung	carcinoma[f]	19/46 (P<0.001)
								carcinoma/adenoma[f]	23/46 (P<0.001)
							respiratory system	tumors[g]	25/46 (P<0.001)
Mice/B6C3F1	M	10 ppm[c]	78 wks	78-79 wk	99.3-99.4%	vapor	lung	carcinoma	3/48 (N.S.)
								carcinoma/adenoma	3/48 (N.S.)
							respiratory system	tumors	3/48 (N.S.)
Mice/B6C3F1	M	0 ppm[e] (chamber control)	NA	79 wk	NA	ambient air	lung	carcinoma	0/41 (P<0.001)
								carcinoma/adenoma	0/41 (P<0.001)
							respiratory system	tumors	0/41 (P<0.001)

TABLE 5-2 (cont.)

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[b] (P value)
Mice/B6C3F1	f	40 ppm[c]	90 wk	90-91 wk	99.3-99.4%	vapor	nasal cavity	carcinoma	6/50 (P=0.013)
								tumors[h]	12/50 (P<0.001)
							lung	carcinoma[f]	37/50 (P<0.001)
								carcinoma/adenoma[f]	41/50 (P<0.001)
							respiratory system	tumors[g]	42/50 (P<0.001)
							subcutaneous tissue or rib	fibrosarcoma	11/50 (P<0.001)
							circulatory system	hemangiosarcoma	23/50 (P<0.001)
								hemangiosarcoma/ hemangioma	27/50 (P<0.001)
							mammary gland	adenocarcinoma	8/50 (P=0.046)
Mice/B6C3F1	f	10 ppm[c]	103 wk	104 wk	99.3-99.4%	vapor	nasal cavity	carcinoma	0/50 (N.S.)
								tumors	0/50 (N.S.)
							lung	carcinoma	5/49 (N.S.)
								carcinoma/adenoma	11/49 (P=0.045)
							respiratory system	tumors	11/49 (P=0.045)
							subcutaneous tissue or rib	fibrosarcoma	5/50 (P<0.028)
							circulatory system	hemangiosarcoma	11/50 (P<0.001)
								hemangiosarcoma/ hemangioma	12/50 (P<0.001)
							mammary gland	adenocarcinoma	14/50 (P=0.001)

TABLE 5-2 (cont.)

Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[b] (P value)
Mice/B6C3F1	F	0 ppm[e] (chamber control)	NA	104-106 wk	NA	ambient air	nasal cavity	carcinoma	0/50 (P=0.001)
								tumors	0/50 (P<0.001)
							lung	carcinoma	1/49 (P<0.001)
								carcinoma/adenoma	4/49 (P<0.001)
							respiratory system	tumors	4/49 (P<0.001)
							subcutaneous tissue or rib	fibrosarcoma	0/50 (P<0.001)
							circulatory system	hemangiosarcomas	0/50 (P<0.001)
								hemangiosarcoma/ hemangioma	0/50 (P<0.001)
							mammary gland	adenocarcinoma	2/50 (N.S.)

QUALITY OF EVIDENCE

Strength of Study: The compound was administered at two doses levels to two species of animals by a natural route of exposure. Comprehensive pathological examinations were performed.

Comment: Exposure was also associated with hepatic necrosis and toxic nephropathy in rats of either sex, testicular degeneration in male rats, retinal degeneration in female rats, and epithelial hyperplasia of the respiratory system in mice.

[a] NIP, 1982

[b] Incidences of most frequently appearing tumors were tabulated. The probability levels for the Fischer exact and Cochran-Armitage tests are given beneath the incidence of tumors in the treated and control groups, respectively, when P<0.05; otherwise, N.S. (not significant) is indicated.

[c] Exposures were 6 hours/day, 5 days/week.

[d] Includes adenomas, adenocarcinomas, adematous polyps, squamous cell carcinomas, papillary adenomas, squamous cell papillomas, and carcinomas of the nose and nasal cavity.

[e] Control groups also served as controls in the bioassay of 1,2-dibromo-3-chloropropane.

[f] Alveolar/bronchiolar tumors

[g] Includes adenomas, carcinomas, and adenomatous polyps of the bronchus, bronchiole and lung, and alveolar/bronchiolar adenomas and carcinomas.

[h] Includes adenomas, carcinomas, adenomatous polyps, and hemangiosarcomas.

NA = Not applicable

TABLE 5-3

Summary of Inhalation Carcinogenicity Bioassay of 1,2-Dibromoethane[a]

Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity[b] of Compound	Target Organ	Tumor Type	Tumor Incidence (P value)
M	20 ppm[c]	18 mo	18 mo	99%	spleen	hemangiosarcoma	10/48 ($p<0.05$)
					adrenal	carcinoma, pheno-chromocytoma, or cortical adenoma	11/48 ($p<0.05$)
					subcutaneous tissue	mesenchymal tumors	11/48 ($p<0.05$)
M	0 ppm	18 mo	18 mo	NA	spleen	hemangiosarcoma	0/48
					adrenal	carcinoma, pheno-chromocytoma, or cortical adenoma	2/48
					subcutaneous tissue	mesenchymal tumors	3/48
f	20 ppm	18 mo	18 mo	99%	spleen	hemangiosarcoma	6/48 ($p<0.05$)
					adrenal	carcinoma, pheno-chromocytoma, or cortical adenoma	6/48 ($p<0.05$)
					mammary gland	adenoma, fibro-adenoma, carcinoma or adenocarcinoma	25/48 ($p<0.05$)

TABLE 5-3 (cont.)

Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity[b] of Compound	Target Organ	Tumor Type	Tumor Incidence (P value)
F	0 ppm[c]	18 mo	18 mo	NA	spleen	hemangiosarcoma	0/48
					adrenal	carcinoma, pheno-chromocytoma or cortical adenoma	1/48
					mammary gland	adenoma, fibro-adenoma, carcinoma or adenocarcinoma	2/48

QUALITY OF EVIDENCE

Strength of Study: The compound was administered by a natural route of exposure for a significant portion of the lifespan. Adequate numbers of rats of both sexes were treated. Thorough histopathological examination was performed.

Overall adequacy: Limited.

Comment: This study was initiated to investigate the combined effects of inhalation exposure of 1,2-dibromoethane and dietary disulfiram. These data are derived from control groups used in that study.

[a]Wong et al., 1982

[b]Physical state was vapor in all cases.

[c]Exposures were 7 hours/day, 5 days/week.

TABLE 5-4

Summary of Inhalation Carcinogenicity Study of 1,2-Dibromoethane in B6C3F1 Mice[a,b]

Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Tumor Type	Tumor Incidence (P value)
M	40 ppm[c]	90 wk	91 wk	99.3%	vapor	papillomas[d] carcinomas sarcomas	3/46 0/46 0/46
M	10 ppm[c]	103 wk	104 wk	99.3%	vapor	papillomas carcinomas sarcomas	0/44 0/44 0/44
M	0 ppm[c]	NA	104 wk	NA	NA	papillomas carcinomas sarcomas	0/45 0/45 0/45
F	40 ppm[c]	90 wk	91 wk	99.3%	vapor	papillomas[d] carcinomas[e] sarcomas[f]	7/49 7/49 2/49
F	10 ppm[c]	103 wk	104 wk	99.3%	vapor	papillomas carcinomas sarcomas[g]	0/49 0/49 1/49
F	0 ppm[c]	NA	104 wk	NA	NA	papillomas carcinomas sarcomas	0/50 0/50 0/50

TABLE 5-4 (cont.)

QUALITY OF EVIDENCE	
Strength of Study:	The compound was administered by a natural route of exposure for a significant portion of the lifespan. Two dose levels and adequate numbers of mice of both sexes were treated.
Overall Adequacy:	Adequate.
Comment:	This study was initated to describe characteristics of ethylene dibromide-induced mouse nasal cavity tumors (other tissues were not examined).

[a]Stinson et al., 1981

[b]The target area in each case was the nasal cavity.

[c]Exposures were 6 hours/day, 5 days/week.

[d]Squamous papillomas

[e]Includes 2 squamous carcinomas, 2 adenocarcinomas and 3 mixed carcinomas

[f]Hemangiosarcoma

[g]Poorly differentiated sarcoma

NA = Not applicable

TABLE 5-5

Summary of Carcinogenicity Study of 1,2-Dibromoethane in Ha:ICR Swiss Mice[a,b]

Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
50 mg/application[c]	3 times/wk for 440-594 days	440-594 days[d]	pure[e]	0.2 mℓ acetone	skin	papilloma	8/30 (P<0.001)
						carcinoma	3/30
					lung	papilloma	26/30 (P<0.0005)
						carcinoma	0/30
					forestomach	papilloma	3/30
						carcinoma	0/30
25 mg/application	3 times/wk for 440-594 days	440-594 days[d]	pure[e]	0.2 mℓ acetone	skin	papilloma	2/30
						carcinoma	2/30
					lung	papilloma	24/30 (P<0.005)
						carcinoma	0/30
					forestomach	papilloma	3/30
						carcinoma	1/30
0 mg (vehicle control)	NR	NR	NA	0.1 mℓ acetone	skin	papilloma	0/30
						carcinoma	0/30
					lung	papilloma	11/30
						carcinoma	0/30
					forestomach	papilloma	2/30
						carcinoma	0/30

TABLE 5-5 (cont.)

Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
0 mg (no treatment)	NA	NR	NA	NA	skin	papilloma	0/100
						carcinoma	0/100
					lung	papilloma	30/100
						carcinoma	0/100
					forestomach	papilloma	5/100
						carcinoma	0/100
75 mg/single application	5 µg PMA, 3 times/wk for 428-576 days[f]	428-576 days[g]	pure[e]	0.2 mℓ acetone (EDB and PMA)	skin	papilloma	2/30
						carcinoma	0/30
2.5 µg PMA (positive control)	3 time/wk for 376 days	376 days[h]	NR	0.2 mℓ acetone	skin	papilloma	9/120
						carcinoma	10/120
5 µg PMA (positive control)	3 times/wk for 376 days	376 days[h]	NR	0.2 mℓ acetone	skin	papilloma	6/90
						carcinoma	7/90

TABLE 5-5 (cont.)

QUALITY OF EVIDENCE	
Strength of Study:	Lifetime duration.
Weakness of Study:	Histopathologic examinations were only performed on skin, liver, stomach, kidneys and abnormal appearing tissues.
Overall Adequacy:	Adequate, but of limited usefulness for quantitative risk estimation.

[a]Van Duuren et al., 1979

[b]In all cases mice were female.

[c]Maximum tolerated dose

[d]Duration for 15 halohydrocarbons, including EDB, ranged from 440-594 days; median survival range was 317 to >589 days.

[e]Purity assayed by NMR

[f]EDB was administered to dorsal skin once, followed 14 days later by PMA 3 times weekly.

[g]Range of median survival time for 15 halohydrocarbons, including EDB.

[h]Median survival time

PMA = Phorbol myristate acetate; NR = Not reported; NA = Not applicable

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5.1.1.2. **INHALATION EXPOSURE** -- Chronic exposure to 1,2-dibromoethane vapors at levels of 10 or 40 ppm caused increased incidences of nasal cavity carcinomas and adenocarcinomas in F344 rats of both sexes and alveolar/bronchiolar carcinomas in female F344 rats and B6C3F1 mice of both sexes (NTP, 1982). Also, chronic inhalation exposure of 1,2-dibromoethane was associated with circulatory system hemangiosarcomas in both sexes of rats, mammary gland fibro-adenomas in female rats, adenocarcinomas of the mammary gland of female mice, fibrosarcomas in the subcutaneous tissues of female mice, and mesotheliomas of the tunica vaginalis of male rats (Table 5-2).

Wong et al. (1982) investigated the carcinogenic effects on rats of inhalation exposure to 1,2-dibromoethane. The complete study is reviewed in Section 5.5 and the data from the 1,2-dibromoethane exposure group and a control group are compared here to evaluate the carcinogenic potential of 1,2-dibromoethane (Table 5-3). Chronic inhalation of 20 ppm 1,2-dibromoethane vapor for 18 months was found to significantly increase the incidence of splenic hemangiosarcomas and tumors of the adrenal glands in both sexes, subcutaneous mesenchymal tumors in males, and mammary tumors in females over controls exposed to clean filtered air.

The carcinogenic potential of 1,2-dibromoethane in the nasal cavities of mice following chronic inhalation exposure in B6C3F1 rats was investigated by Stinson et al. (1981) and is summarized in Table 5-4. An elevated incidence of nasal cavity carcinomas over controls appears to have occurred in female mice exposed to a 1,2-dibromoethane concentration of 40 ppm. Neither sex had elevated tumor incidence at 10 ppm. The statistical significance of this observation is not clear, as no probability values were reported.

5.1.1.3. **DERMAL EXPOSURE** -- Van Duuren et al. (1979) reported increased incidences of local and distant papillomas in mice that received

dermal applications of 1,2-dibromoethane for up to 594 days (Table 5-5). The dermal application of 1,2-dibromoethane in a single dose followed by thrice weekly promotion with phorbol myristate (PMA), however, did not result in an increased incidence of local papillomas.

5.1.2. **Human Studies.** The mortality experience of 161 1,2-dibromoethane production plant workers was compared to that of the United States white male general population (Ott et al., 1980). Neither total deaths nor total malignancies of individuals exposed to 1,2-dibromoethane were found to exceed the control rate. The significance of this study is unknown because of the small number of cancer deaths and the poorly characterized exposure conditions.

5.2. MUTAGENICITY

Malling (1969) first reported the mutagenic properties of 1,2-dibromoethane in a recessive lethal assay using Neurospora crassa.

The mutagenic activity of 1,2-dibromoethane has been reviewed by Fahrig (1974), IARC (1977) and Rannug (1980) (Table 5-6).

Positive results in reverse mutation assays have been reported in the indicator organism, Salmonella typhimurium strains G46, TA1530, TA1535 and TA100 (Buselmaier, 1973; Brem, 1974; Ames, 1971; Rannug et al., 1978; Stolzenberg and Hine, 1980; Van Bladeren et al., 1980; Principe et al., 1981; Shiau et al., 1980) both with and without metabolic activation. Reduced (Barber et al., 1981) or negative mutagenic activity in the S. typhimurium strains TA1538 and TA98 (Brem, 1974; Principe et al., 1981) also has been observed.

TABLE 5-6

Mutagenicity of 1,2-Dibromoethane

Assay	Indicator Organism	Concentration	Application	Activating System	Response	Comment	Reference
Recessive lethals	D. melanogaster Berlin K	0.3 mM for 3 days	NR	NA	+	1.1% treated 0.27% control	Vogel and Chandler, 1974
Recessive lethals	D. melanogaster	0.2 ppm for 11 hours	vapor	NA	+	4 times spontaneous rate	Kale and Baum, 1979
Recessive lethals	N. crassa ad-3 mutants	NR	liquid holding	NA	+	NC	Malling, 1969
Reverse mutation	S. typhimurium his G-46 and TA1530	5 µl/plate	spot test	NR	+	NC	Ames, 1971
Reverse mutation	S. typhimurium TA1530, TA1535	10 µM/plate	plate incorporation	-	+	NC	Brem, 1974
Reverse mutation	S. typhimurium TA 1538	10 µM/plate	plate incorporation	-	-	NC	Brem, 1974
Reverse mutation	S. typhimurium TA 1535	0.5-2.0 µM/plate	plate incorporation	± Rat S-9	+	NC	Rannug et al., 1978
Reverse mutation	S. typhimurium G 46	NR	disc	-	+	NC	Buselmaier, 1973
Reverse mutation	S. typhimurium G 46	500 mg/kg	NMRI-s.c. injection	+	+	NC	Buselmaier, 1973
Reverse mutation	S. typhimurium TA100	0.1, 1 µM/plate	disc	± Rat S-9	+	more active with S-9	Stolzenberg and Hine, 1980
Reverse mutation	S. typhimurium TA100	1-4 mM	plate incorporation	± Rat S-9	+	more active with S-9	Van Bladeren et al., 1980
Reverse mutation	S. typhimurium TA1535	1.7 ppm	vapor	± Rat S-9	+	lowest concentration to mutate	Barber et al., 1981
Reverse mutation	S. typhimurium TA98	24.8 ppm	vapor	± Rat S-9	+	lowest concentration to mutate	Barber et al., 1981

TABLE 5-6 (cont.)

Assay	Indicator Organism	Concentration	Application	Activating System	Response	Comment	Reference
Reverse mutation	S. typhimurium TA100	4.3 ppm	vapor	± Rat S-9	+	lowest concentration to mutate	Barber et al., 1981
Reverse mutation	S. typhimurium TA1535	300 µg/plate	disc	-	-	NC	Shiau et al., 1980
Reverse mutation	S. typhimurium TA1535	100 µg/plate	disc	+	+	NC	Shiau et al., 1980
Reverse mutation	B. subtilis TKJ5211 and TKJ6321	300 µg/plate	disc	-	-	NC	Shiau et al., 1980
Reverse mutation	B. subtilis TKJ5211 and TKJ6321	50 µg/plate	disc	+ Rat S-9	+	NC	Shiau et al., 1980
Reverse mutation	E. coli WP2 uvrA	20-10,000 µM	plate incorporation	-	+	NC	Hemminki et al., 1981
Forward mutation	S. coelicolor	100 µl/plate	spot test	-	+	NC	Principe et al., 1981
Forward mutation	A. nidulans haploid 35	200 µl/plate	spot test	-	+	NC	Principe et al., 1981
Forward mutation	mouse lymphoma cells	<3 mM for 2 hours	medium	-	+	as effective as 600R X rays	Clive, 1973
Forward mutation	Chinese hamster ovary HGPRT system	0.05-3 mm	liquid	± Rat S-9	+	NC	Tan and Hsie, 1981
DNA modification	E. coli pol A+, pol A-	10 µl/plate	disc	-	+	NC	Brem, 1974
Sister chromatid exchange	Chinese hamster cell culture	0.5-5 mM for 26.5 hours	liquid	-	+	NC	Tezuka et al., 1980
Chromosomal aberrations	Chinese hamster cell culture	2-5 mM for 26.5 hours	NR	-	+	NC	Tezuka et al., 1980

TABLE 5-6 (cont.)

Assay	Indicator Organism	Concentration	Application	Activating System	Response	Comment	Reference
Sister chromatid exchange	human lymphocytes	10 nM-1mM	liquid	± Rat S-9	+	enhanced by S-9	Geddes, 1982
DNA repair	rat hepatocytes	10 ppm	liquid	NA	+	cytotoxic at ≥50 ppm	Williams et al., 1982
Dominant lethal	SD rat C57BLX DBA/2	10 or 30 mg/kg for 5 days	gavage	NA	-	NC	Teramoto et al., 1980
Dominant lethal	mouse	100 or 150 mg/kg/day for 5 days	gavage	NA	-	NC	Teramoto et al., 1980
Dominant lethal	rat	19 or 39 ppm	vapor	NA	-	NC	Short et al., 1979
Dominant lethal	mouse	50 or 150 mg/kg/day for 5 days	gavage	NA	-	NC	Epstein et al., 1972
Dominant lethal	mouse	18 or 90 mg/kg	i.p.	NA	-	NC	Epstein et al., 1972

NA = Not applicable; NC = No comment; NR = Not reported

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In Drosphila melanogaster, the incidence of recessive lethal mutations has been found to exceed the spontaneous rate after exposure to 1,2-dibromoethane vapor (Vogel and Chandler, 1974; Kale and Baum, 1979, 1982).

Shiau et al. (1980) reported that 1,2-dibromoethane induced reverse mutations in Bacillus subtilis in the presence of rat liver microsomal enzymes, but results were negative without microsomal enzymes even at 6 times the concentration used in the positive assay.

Mutagenic activity of 1,2-dibromoethane in E. coli has been observed in the absence of metabolic activation. Brem (1974) has demonstrated the DNA modifying ability of 1,2-dibromoethane by comparing its effect on the growth inhibition of E. coli pol A^- with that of E. coli pol A^+. The preferential inhibition of growth seen in the DNA polymerase deficient (pol A^-) strain indicates that DNA damage has occurred. Hemminki et al. (1981) have reported induction of reverse mutations in E. coli treated with 1,2-dibromoethane without metabolic activation.

Principe et al. (1981) reported that 1,2-dibromoethane induced forward mutations in Streptomyces coelicolor and Aspergillus nidulans in a spot test at 100 and 200 µl/plate, respectively.

Several authors have reported the genetic activity of 1,2-dibromoethane in mammalian cell culture assay systems. Tezuka et al. (1980) have investigated 1,2-dibromoethane mutagenicity in Chinese hamster cell cultures, and observed induction of sister chromatid exchange and chromosomal aberrations at concentrations <5 mM in the absence of microsomal activation. Geddes (1982) found that 1,2-dibromoethane induced sister chromatid exchange in human lymphocytes in vitro, especially in the presence of rat liver microsomal activation.

Clive (1973) induced forward mutations in cultured mouse lymphoma cells with 1,2-dibromoethane without mammalian activation, and reported that a 3 mM concentration produced mutations as effectively as 600 R X rays.

DNA damage measured *in vitro* as the amount of repair synthesis was found to occur in non-replicating rat hepatocytes incubated in 10 ppm 1,2-dibromoethane (Williams et al., 1982). In autoradiography an increased number of nuclear grains produced after incubation of the treated cells with labeled thymidine was interpreted as induction of DNA repair synthesis.

Induction of forward mutations by 1,2-dibromoethane was reported by Tan and Hsie (1981) in Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) system. Mutagenicity was unaffected by the addition or omission of a metabolic activation system.

A great deal of evidence exists to implicate 1,2-dibromoethane as an alkylating agent capable of crosslinking and binding to biomacromolecules. Protein binding has been demonstrated using radiolabeled 1,2-dibromoethane in various tissues such as stomach and hepatic microsomal proteins (Banerjee and Van Duuren, 1979) *in vitro*; and liver, kidney, intestines, heart, lung, brain, testes and stomach macromolecules (protein > RNA > DNA) (Hill et al., 1978) *in vivo*.

Conjugation of 1,2-dibromoethane with glutathione to a more mutagenic intermediate has been accomplished *in vitro* with rat liver S-9 in the presence of glutathione (Van Bladeren et al., 1980).

The mutagenicity of 1,2-dibromoethane in plants has been thoroughly investigated by several authors. Induction of chlorophyll mutations in barley (Ehrenberg et al., 1974), somatic mutations in *Tradescantia* (Schairer

et al., 1978; Nauman, 1978; Ma et al., 1978) and the bioactivation of 1,2-dibromoethane to a more mutagenic agent by Tradescantia extract (Scott et al., 1978) have been reported.

While evidence suggests that 1,2-dibromoethane metabolites induce mutations, there have been no reports of dominant lethal mutations occurring in mammalian systems in vivo. Administration by gavage (Teramoto et al., 1980; Epstein et al., 1972), inhalation (Short et al., 1979) or i.p. injection (Epstein et al., 1972) failed to induce dominant lethal mutations in rats and mice.

Oral administration of 1,2-dibromoethane to bulls reduced sperm count and motility (Amir, 1965) and increased the production of abnormal sperm (Amir, 1973; 1975). These effects were reversible upon discontinuation of treatment, but upon retreatment the effects were longer lasting (Amir and Volcani, 1965). It is difficult to interpret effects following oral administration of toxicants to ruminants because of their different digestive systems.

The mutagenicity of 1,2-dibromoethane has been demonstrated in most of the microbial and cellular culture assay systems used, but negative in dominant lethal assays in vivo.

5.3. TERATOGENICITY

The Registry of Toxic Effects of Chemical Substances lists 1,2-dibromoethane as a teratogen (NIOSH, 1983). Short et al. (1976, 1978, 1979) and Minor et al. (1978) observed equivocal evidence of embryotoxicity in CD-1 mice and Charles River CD rats wherein mated females (Short et al., 1976, 1978) were exposed to 1,2-dibromoethane vapors during organogenesis. Adverse developmental effects were observed, but reduced maternal food

intake and body weight gains confound the interpretation of these results. Male and female rats exposed to 1,2-dibromoethane vapors prior to mating had toxic effects, but produced normal litters.

Short et al. (1976) exposed previously mated female rats and mice, 28/group, to 32 ppm 1,2-dibromoethane vapors on days 6-16 of gestation. Day 0 of gestation was the day on which sperm-positive vaginal smears or copulation plugs were observed. Control groups consisted of 18 rats or 20-24 mice who received no vapor exposure and a normal or restricted diet. Food consumption and body weights were recorded. On days 18 and 20 of gestation, mice and rats, respectively, were killed and the fetuses examined histopathologically.

Mortality was unaffected by exposure or diet, but decreased body weight gain and food consumption were observed in exposed animals. Incidences of wavy and extra ribs and hydrocephaly in fetuses from exposed rats were significantly different from controls. Increased incidences of unossified sternebrae were observed in fetuses from exposed and restricted diet mice and were significantly different from controls. Incidences of incomplete ossification of the supraoccipital bones and complete lack of ossification of the incus in fetuses from exposed mice were significantly different from controls. These anomalies also occurred in fetuses from restricted diet mice, but the incidences were not significantly different from controls. No other anomalies were observed that could be ascribed to treatment.

Short et al. (1978) conducted a similar reproductive study using three exposure levels of 1,2-dibromoethane. Groups of 16 female rats and 20 female mice were mated and exposed to 0 (diet ad libitum), 0 (diet restricted), 20, 38 or 80 ppm 1,2-dibromoethane vapors 23 hours/day on days 6-16 of gestation. The day on which copulation plugs or the presence of sperm in

vaginal smears was observed was taken as day 0 of gestation. Food consumption and body weights were recorded. On days 18 and 20 of gestation, mice and rats, respectively, were killed and the fetuses examined histopathologically.

Increased mortality of adult rats occurred at the 80 ppm exposure level, 8/16 vs. 0/17 for controls. No live pups or viable fetuses were obtained from dams at this exposure level, but normal numbers of births were seen at lower levels. Reduced food consumption was observed in all exposed groups, with reduced body weight gains in rats exposed to $\geq$38 ppm or on the restricted diet.

A statistically significant decrease in the percentage of fetuses with normally ossified centrae was observed at 20 ppm, but not 38 ppm. Some soft tissue abnormalities occurred in the fetuses of exposed rats, but were not statistically significant. All exposed mice had reduced body weight gain with reduced food consumption. Maternal mortality was reduced in feed-restricted mice and those exposed at levels $\geq$38 ppm. Statistically significant incidences of certain skeletal abnormalities (i.e., unossified incus and incomplete supraoccipital ossification) occurred in mice exposed to $\geq$20 ppm, but it is unclear whether this is a result of treatment or malnutrition.

To further examine the effects of inhaled 1,2-dibromoethane on reproduction in rats, Short et al. (1979) exposed both sexes of Charles River CD rats prior to mating. Groups of 18 or 20 male rats were exposed to 19, 38 or 89 ppm 1,2-dibromoethane vapors 7 hours/day, 5 days/week for 10 weeks. Half of the males were killed after exposure and their serum testosterone and testes were examined. The remaining exposed males were mated to females who had been exposed to 0, 20, 39 or 80 ppm 1,2-dibromoethane vapors 7 hours/day, 7 days/week for 3 weeks. Dams were killed after 3 weeks of

gestation and the pups were examined histopathologically. Evidence of toxicity at the highest exposure level was found in adults of both sexes (i.e., reduced body weight gain and food consumption, female mortality and male testicular atrophy), but no adverse effects were observed in the litters from any exposure group.

Hardin et al. (1981) reported the absence of teratogenicity of 1,2-dibromoethane after i.p. injection. Groups of 10-15 inseminated female Sprague-Dawley rats received 55 mg 1,2-dibromoethane/kg on days 1-15 of gestation. The day on which sperm-positive vaginal lavage was observed was taken as day 1 of gestation. On day 21 the females were killed and histopathological examination was performed on the dams and fetuses. No gross internal or external fetal malformations were observed, but there was evidence of maternal toxicity (reduced maternal weight gain).

It appears that inhalation of 1,2-dibromoethane may be weakly teratogenic, but only at concentrations that also produce material toxicity. Therefore, it is difficult to reach a definite conclusion regarding whether these results represent a teratogenic effect of 1,2-dibromoethane or delayed development resulting from maternal toxicity.

5.4. OTHER REPRODUCTIVE EFFECTS

5.4.1. Animal Studies. Short et al. (1979) reported adverse effects of 1,2-dibromoethane on the adult rats used in the previously described reproduction study. Males exposed to 89 ppm 1,2-dibromoethane had reduced food consumption, reduced serum testosterone concentrations and atrophy of the reproductive organs, and failed to impregnate any females, while females exposed to 80 ppm had abnormal estrous cycles during exposure. These adverse conditions were absent in males and females exposed to lower concen-

trations of 1,2-dibromoethane. It is uncertain whether the observed reproductive effects are attributable to 1,2-dibromoethane exposure or to malnutrition.

The effects of 1,2-dibromoethane on the fertility of male Wistar rats were reported by Edwards et al. (1970). Males received 5 daily doses of 5 mg 1,2-dibromoethane/kg by i.p. injection prior to mating to 6 female rats 1/week for 10 weeks. Infertility was observed in the 4th week of mating and returned to normal in the following weeks, which is indicative of spermatid damage.

Many authors have reported the antifertility effects of 1,2-dibromoethane on bulls (e.g., Courtens et al., 1980; Amir, 1973, 1975), rams (e.g., Sastry and Mukhergee, 1980; Hrudka and Eljack, 1979) and chickens (Bondi et al., 1955; Alumot et al., 1968).

5.4.2. Human Studies. Wong et al. (1979) conducted a retrospective study to examine the reproductive performance of 297 workers in four 1,2-dibromoethane production facilities. Men who had been exposed (<0.5-5 ppm) to 1,2-dibromoethane and their wives were used to calculate standardized birth ratios which were compared to expected birth ratios from national fertility tables. When pooled, the observed/expected births ratio for all four facilities was not significantly different from unity. When examined individually, the observed/expected births ratio at one plant was significantly low, but the prevalence of vasectomy was higher than average.

As reported by NIOSH (1977b), medical examinations were performed on 26 production workers exposed to 1,2-dibromoethane and 9 unexposed (control) workers. Detectable levels of 1,2-dibromoethane were not found upon environmental sampling at the plant. Blood and semen samples taken from the subjects had serum testosterone, serum follicle stimulating hormone and

sperm count values not different from controls. However, a statistically significant ($0.02 > p > 0.01$) decrease in leutenizing hormone levels was observed in the exposed group. Rogers et al. (1981) evaluated the effect of 1,2-dibromoethane on fertility impairment in three male populations. The populations consisted of 16 exposed agricultural workers, 39 persons exposed to 1,2-dibromoethane contaminated wellwater (300 ppb) and 28 non-exposed (control) individuals. Serum leutenizing and follicle stimulating hormone levels, sperm morphology and sperm motility were not significantly different among the three populations. The percentages of abnormally low sperm counts, however, for the worker, well water and control populations were 34.2, 43.8 and 17.8%, respectively. Takahashi et al. (1981) compared sperm counts in samples from 13 men occupationally exposed to 1,2-dibromoethane and dibromochloropropane for an average of 2.8 years with a control population of 19 men without 1,2-dibromoethane exposure. Significant reductions in sperm counts were observed in the exposed group, but the results are confounded due to the simultaneous exposure of dibromochloropropane.

Ter Haar (1980) reported the absence of reduced sperm counts in 59 1,2-dibromoethane production workers. Sperm count values from men exposed to <0.5 or 0.5-5 ppm were found to have a similar distribution as compared to the values found in the literature. The levels and duration of exposure were not reported.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Reznick et al. (1980) conducted a subchronic 1,2-dibromoethane inhalation study in F344 rats and B6C3F1 mice to identify a maximum tolerated exposure level. Groups of 5 rats and 10 mice of both sexes were exposed to atmospheres containing 0, 3, 15 or 75 ppm 1,2-dibromoethane for 6 hours/day, 5 days/week for 13 weeks. All animals surviving treatment and those found

dead or moribund were examined histopathologically. Nasal cavity alterations such as cytomegaly, focal hyperplasia, squamous metaplasia and loss of cilia were observed in the high exposure groups of both species, but were absent in the control and medium and low exposure groups. No lesions were observed in other tissues.

Rowe et al. (1952) reported the absence of adverse effects in groups of 40 rats (20 of each sex), 16 guinea pigs (8 of each sex), 4 rabbits (3 male and 1 female) and 2 monkeys (1 of each sex) exposed to 0 or 25 ppm 1,2-dibromoethane vapors by inhalation 7 hours/day, 5 days/week for 6 months. The toxicological parameters investigated were general appearance and behavior, growth rate, organ and body weights, blood urea nitrogen values and tissue lesions. High mortality was observed in both exposed and control groups. Similar groups of animals were exposed to 50 ppm 1,2-dibromoethane vapors, 7 hours/day, 5 days/week for 70-90 days. Following exposure, rats had increased liver and kidney weights (both sexes), increased lung weights (males) decreased spleen weights (females) and decreased testicular weights. Guinea pigs had decreased body weight gain, slight central fatty degeneration of the liver and renal tubular epithelium degeneration. Rabbits and monkeys had slight increases in liver weights.

Toxic effects of 1,2-dibromoethane in rats and mice were reported in the carcinogenesis bioassays using gavage (NCI, 1978) and inhalation (NTP, 1982) as the modes of administration (see Tables 5-1 and 5-2).

Gavage administration of 1,2-dibromoethane to rats for 49-61 weeks resulted in hyperkeratosis and acanthosis of the forestomach, peliosis hepatitis, degeneration of adrenal cortical cells and testicular atrophy at dosages of ~28 mg/kg/day (NCI, 1978). Similar lesions were observed in mice given ~76 mg/kg/day, but not 44 mg/kg/day for 78 weeks.

Rats exposed to 40 or 10 ppm 1,2-dibromoethane 6 hours/day, 5 days/week by inhalation for 88-91 weeks developed nasal cavity hyperplasia, toxic nephropathy and testicular degeneration which was not present in controls (NTP, 1982). Mice exposed to 40 or 10 ppm 1,2-dibromoethane 6 hours/day, 5 days/week by inhalation for 78-103 weeks developed nasal cavity inflammation and epithelial hyperplasia of the alveoli and bronchial tract especially at the high concentration (NTP, 1982; Stinson et al., 1981).

Much has been reported regarding the enhanced toxicity and carcinogenicity of 1,2-dibromoethane with concurrent disulfiram exposure. Modification of 1,2-dibromoethane biotransformation by disulfiram, an acetaldehyde dehydrogenase inhibitor, is thought to result in greater toxicity from buildup of 1,2-dibromoethane and its metabolites. The effects of 1,2-dibromoethane inhalation exposure with and without dietary administration of disulfiram were examined in the rat by Wong et al. (1982). Four groups of 48 male and 48 female Sprague-Dawley rats were given a control diet and no vapor exposure, a 0.05% disulfiram diet and no vapor exposure, a control diet and exposure to 20 ppm 1,2-dibromoethane or a 0.05% disulfiram diet and exposure to 20 ppm 1,2-dibromoethane. The exposures occurred 7 hours/day, 5 days/week for 18 months. Clinical signs, body weights, hematology and histopathological evaluations were examined to determine the effects of the treatments. The following observations were found to have statistical significance over controls: increased incidence of liver, spleen, mesentary, kidney, adrenal, thyroid, mammary tumors, decreased testicular weights, decreased erythrocyte count, hematocrit and hemoglobin in the 1,2-dibromoethane/disulfiram group; increased incidence of splenic atrophy (males), hemosiderosis (males), hemangiosarcoma, adrenal tumors, subcutaneous mesen-

chymal tumors (males) and mammary tumors in the 1,2-dibromoethane/control diet group; and increased incidences of splenic hemosiderosis and mammary tumors in females of the control air/disulfiram diet group.

5.6. OTHER RELEVANT INFORMATION

Acute exposure to 1,2-dibromoethane can adversely affect the kidney, liver, heart and other internal organs and systems (Rowe et al., 1952; Kluwe et al., 1982). Skin contact can cause chemical burns as well as systemic effects. Much has been written concerning the interaction of disulfiram and 1,2-dibromoethane. Enhanced toxicity and carcinogenicity have been observed upon simultaneous exposure to both compounds (Plotnick, 1979; Wong et al., 1982). This toxic interaction can occur in the workplace, as disulfiram is used in the treatment of alcoholism. Stein et al. (1978) have suggested that precautions should be taken so that no worker is exposed to both of these agents.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The lethality of 1,2-dibromoethane was examined in acute static toxicity tests (with aeration) in bluegill sunfish, Lepomis macrochirus, and largemouth bass, Micropterus salmoides (Davis and Hardcastle, 1959). The 24-hour LC_{50} values tested in soft water and water of medium hardness (19.0 and 77.1 mg/ℓ) were 25 and 18 mg/ℓ for the sunfish and 25 and 15 mg/ℓ for the bass, respectively. The 48-hour LC_{50} values for sunfish and bass tested in the soft water (19.0 mg/ℓ; 25°C; 256.8 mg/ℓ dissolved solids) were 18 and 15 mg 1,2-dibromoethane/ℓ, respectively.

In goldfish, Carassius auratus, exposed to 1 mg 1,2-dibromoethane/ℓ for up to 10 hours, a bioconcentration coefficient of 0.714 was reported (Ogino et al., 1978). An equilibrium between tissue and water levels was reached within 5 hours, and the biological half-life for 1,2-dibromoethane was reported to be 30 minutes (Ogino, 1978; Ogino et al., 1978).

6.2. CHRONIC EFFECTS

Pertinent data regarding the chronic effects of 1,2-dibromoethane on aquatic organisms were not located in the available literature.

6.3. PLANT EFFECTS

Pertinent data regarding the effects of 1,2-dibromoethane exposure on aquatic plants were not located in the available literature.

6.4. RESIDUES

Pertinent data regarding residues of 1,2-dibromoethane in the aquatic environment were not located in the available literature. As noted previously, the bioconcentration coefficient of this compound was reported to be 0.714 in goldfish (Ogino et al., 1978).

6.5. OTHER RELEVANT INFORMATION

Other relevant data on the aquatic toxicity of 1,2-dibromoethane were not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMANS

The Occupational Safety and Health Administration (OSHA) has lowered the 8-hour TWA exposure limit from 20 ppm to 0.1 ppm. The new short-term exposure limit (STEL) is 0.5 ppm over 30 minutes (Federal Register, 1983b). The National Institute for Occupational Safety and Health recommends a 0.13 ppm STEL, and the American Conference of Governmental Industrial Hygienists has given 1,2-dibromoethane an A2 (suspected carcinogen) rating.

The U.S. EPA (1983a) has recently suspended the use of the pesticide 1,2-dibromoethane as a soil fumigant and is limiting the use of this substance in fumigation of citrus fruits. The tolerances for 1,2-dibromoethane on food products have been set at 900 ppb for raw grain for human consumption, 150 ppb for flour and 30 ppb for ready-to-eat products.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of 1,2-dibromoethane were not located in the available literature.

8. RISK ASSESSMENT

Upon review of the available data, it is evident that 1,2-dibromoethane is toxic and carcinogenic in laboratory animals and mutagenic in a variety of microbial and cell culture assays. The most important aspect of the effects of exposure is the possibility of increased cancer in the exposed population. Because 1,2-dibromoethane is widely used as a fumigant and gasoline additive, the population at risk is potentially large.

Carcinogenicity bioassays in laboratory animals can provide a basis for estimating the carcinogenic risk of 1,2-dibromoethane to humans. Several studies have demonstrated the carcinogenicity of 1,2-dibromoethane in rodents exposed by inhalation (NTP, 1982; Wong, 1982; Stinson et al., 1981), oral intubation (NCI, 1978) and dermal application. Because unequivocal evidence of carcinogenicity in man from 1,2-dibromoethane exposure is not available, reliance must be placed on animal studies for assessment of the risks for humans.

The clearest evidence of a potential cancer risk due to ingestion of EDB is found in NCI's TRS, No. 86, 1978 report. A high incidence of forestomach carcinoma was observed in all exposure-species-sex groups in a relatively short period of time.

To make use of this data a mathematical model that incorporated variable partial lifetime exposure was developed. The details of this model are explained in a paper by Thorslund (1982) presented at the Pacific Division AAAS meeting in Santa Barbara, California.

In that paper a human risk at age t due to an exposure of d mg/kg/day from age s to f was estimated from the equation

$$P(t,d) = 1-e^{-6.958 \times 10^{-14} \times d \times [(t-s)^{7.6}-(t-f)^{7.6}]}$$

However, that equation was based upon an equivalency assumption between species on a mg/kg basis. Assuming mg/surface area exposure equivalency, 70 kg human and a 500 g rat, the exponent in the above equation is multiplied by $(70/0.5)^{1/3} = 5.192$ which gives the result:

$$P(t,d) = 1-e^{-3.613 \times 10^{-13} \times d \times [(t-s)^{7.6}-(t-f)^{7.6}]}$$

To estimate the exposure level of 1,2-dibromoethane that will result in a specified risk P(t,d) we solve the above equation for d giving the result

$$d = -\ln[1-P(t,d)]/(3.613 \times 10^{-13} \times [(t-s)^{7.6} - (t-f)^{7.6}]).$$

Using a median lifespan of 76.2 years and assuming a 70 kg body weight, the daily dose associated with the following lifetime increases in cancer risk are estimated as follows:

Risk Level	Dose (mg/day)
10^{-5}	1.04×10^{-5}
10^{-6}	1.04×10^{-6}
10^{-7}	1.04×10^{-7}

9. REFERENCES

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. TLVs: Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981). Cincinnati, OH. 486 p.

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Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, Vol. 2A, 3rd rev. ed. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, Vol. 2B, 3rd rev. ed. John Wiley and Sons, NY. p. 2879-3816.

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Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

Muir, G.D., Ed. 1977. Hazards in the Chemical Laboratory, 2nd ed. The London Chemical Society, London. 473 p.

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Proctor, N.H. and J.P. Hughes. 1978. Chemical Hazards of the Workplace. J.B. Lippincott Co., Philadelphia, PA. 533 p.

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Some of the carcinogenicity summary tables in this profile were adapted from a report [Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of Ethylene Dibromide (106-93-4)] prepared by Syracuse Research Corporation (1983) for the Carcinogen Assessment Group of the U.S. EPA under Contract 68-03-3112.